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Overweight and obesity during adolescence increases the risk of renal cell carcinoma

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While overweight among adults has been linked with renal cell carcinoma (RCC) risk, little is known about the potential influence of overweight and obesity during adolescence. To ascertain if adolescent body mass index is associated with subsequent risk of RCC, we identified a cohort of 238,788 Swedish men who underwent mandatory military conscription assessment between 1969 and 1976 at a mean age of 18.5 years. At the time of conscription assessment, physical and psychological tests were performed including measurements of height and weight. Participants were followed through linkage to the Swedish Cancer Registry to identify incident diagnoses of RCC. The association between body mass index (BMI, kg/m^2) at conscription assessment and subsequent RCC was evaluated using multivariable Cox regression. During a follow-up of up to 37 years, 266 men were diagnosed with RCC. We observed a trend for higher RCC risk with increasing BMI during adolescence, where one-unit increase in BMI conferred a 6% increased risk of RCC (95% CI 1.01–1.10). compared to normal weight men (BMI 18.5- < 25), men with overweight (BMI 25- < 30) or obesity (BMI ≥30) had hazard ratios for RCC of 1.76 (95% CI 1.16–2.67) and 2.87 (95% CI 1.26–6.25), respectively. The link between overweight/obesity and RCC appear to be already established during late adolescence. Prevention of unhealthy weight gain during childhood and adolescence may thus be a target in efforts to decrease the burden of RCC in the adult population.

Key words: renal cell carcinoma, obesity, overweight, adolescence, cancer epidemiology

Abbreviations: RCC: renal cell carcinoma; BMI: body mass index; HIF: hypoxia-inducible factors; SEI: socioeconomic index; ESR: erythrocyte sedimentation rate; EVF: erythrocyte volume fraction; IGF: insulin-like growth factor; VHL: von Hippel–Lindau; DEXA: Dual-energy X-ray absorptiometry

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Introduction

The incidence of renal cell carcinoma (RCC) has increased globally over recent decades, and the underlying reasons are not well understood. RCC accounts for more than 90% of all renal malignancies and a total of 338,000 new cases leads to over 140,000 deaths annually.[1] The global variation in incidence is more than tenfold, and higher incidence rates have been observed in North America and Europe than in Asia and Africa.[1] Geographical differences may be explained both by genetic and environmental factors including access to health care and diagnostic modalities, but the temporal trends for RCC suggest a substantial influence of lifestyle factors.[2,3]

Obesity is a well-established risk factor for RCC in both men and women,[4] but most studies have focused on adults.[5–7] The prevalence of obesity among teenagers has increased dramatically over recent decades,[8] but few studies have yet addressed the potential influence of overweight and obesity in adolescence on RCC risk.

An important role for inflammation in tumorigenesis is now generally accepted and an inflammatory microenvironment is considered an essential component of all tumours.[9] Obesity is considered a state of chronic low-grade systemic inflammation through activation of acute-phase and systemic inflammatory response proteins.[10] Inflammation may contribute to tumour

What's new?

While overweight among adults has been linked with renal cell carcinoma risk, little is known about the potential influence of overweight and obesity during adolescence. This large prospective cohort study over more than 35 years suggests that the link between overweight/obesity—alone and in combination with low physical working capacity—and renal cell carcinoma is already established in late adolescence. Prevention of unhealthy weight gain during childhood and adolescence may thus be a target in efforts to decrease the burden of renal cell carcinoma in the adult population.

initiation and promotion through multiple mechanisms,[9] such as upregulation of hypoxia-inducible factors (HIF) and downregulation of adiponectin.[11]

A better understanding of the role of overweight and obesity earlier in life is needed to target relevant time-windows for prevention efforts. To this end, we aimed to investigate the association between BMI in late adolescence and subsequent risk of RCC in large a national cohort of men in Sweden.

Material and Methods

Our study population consists of a cohort of men, born between 1952 and 1956, who underwent compulsory conscription assessment for Swedish military service between 1969 and 1976 at ages 18–19 years. Men with a severe disability, chronic disease, or if incarcerated were exempt from conscription, leaving >96% of the population eligible. The conscription assessment included standardised physical and psychological examinations and blood tests. The information was recorded in the Swedish Military Service Conscription Register.

Height and weight were measured by trained personnel at the time of conscription examination, from which BMI (kg/m^2) was calculated. BMI was categorised as underweight (<18), normal weight (18 to <25), overweight (25 to <30) and obese (≥30).

Data were collected for the following covariates, chosen for their possible association with exposure and outcome; household crowding, parental socioeconomic index (SEI), systolic and diastolic blood pressure, health status at conscription (summarised in a disease score), erythrocyte sedimentation rate (ESR), erythrocyte volume fraction (EVF), cognitive function, muscular strength and physical working capacity. These variables have been described in detail previously.[12] Briefly, household crowding and parental SEI were collected using data from the Swedish population and housing census. Household crowding was calculated by dividing the number of persons living in a household by the number of habitable rooms. Parental occupation was classified into business owners/managers, farm owner/managers, manual workers, agricultural workers, office workers and other. Resting systolic and diastolic blood pressure was measured using a sphygmomanometer. Physicians collected medical history and classified health status based on the severity of existing health problems. Venous blood samples were analysed for ESR, a non-specific marker of inflammation,[13] and EVF to correct the assessment of inflammation evaluated by ESR. A cognitive function score was calculated from a written assessment testing the potential conscripts' aptitude in linguistic understanding, spatial recognition, general knowledge and ability to follow mechanical instruction. Muscular strength was evaluated by performance on three isometric muscle strength tests, and physical working capacity was assessed using a cycle ergonometric test.

During the study period 284,198 persons went through conscription assessment. We excluded 2,564 persons due to female sex, errors in personal identification number or uncertain vital status. We further excluded 225 men due to improbable measures at conscription assessment, including height < 144 cm, weight > 178 kg, BMI <15, systolic blood pressure < 50 or > 230 mm Hg, diastolic blood pressure < 30 or > 135 mm Hg. Some 31,921 men were excluded because of unknown age or age < 16 or > 20 years. Finally, 22 men were excluded due to unknown illness, 137 men due to extreme weakness, and 10,541 men due to missing data for covariates, leaving 238,788 men in the final sample.

The study was approved by the regional ethical review board, Uppsala, Sweden (decision reference 2014/324).

The cohort members were followed for RCC diagnosis from time of conscription assessment until 1 January 2010. RCC diagnoses were identified by linkage to the Swedish Cancer Registry using the international classification of disease-7 code for RCC (64.9). The Swedish Cancer Registry was established in 1958 and is estimated to have a completeness of 95–97% for common cancer types.[14] Date of emigration and vital status were determined using the Total Population Register.

Cox regression was used to evaluate the association between BMI at conscription and subsequent RCC. Cohort members were followed until the earliest of date of RCC diagnosis, date of death, date of emigration or January 1, 2010. We selected covariates to include in the models based on their association with BMI and with RCC risk. Although not evident from these data, earlier studies have suggested links between RCC risk and blood pressure, cognitive function, chronic inflammation, and physical activity[15,16] The multivariable models were therefore adjusted for blood pressure, cognitive function, ESR/EVF, muscular strength and physical working capacity in addition to some general determinants of disease risk: age, socioeconomic circumstances (household crowding and parental SEI) and earlier disease. A high BMI in young men can indicate either high muscle mass or high fat mass, with different potential implications for the risk of RCC. Aiming to disentangle the underlying mechanisms, we assessed the association between BMI and RCC by physical working capacity – a measure likely to reflect both general fitness and muscle mass.

Results

During follow-up over a mean of 35.4 years, until a maximum age at study exit of 57 years, 266 men in the cohort were diagnosed with RCC. Mean age at baseline was 18.5 years, and mean age at RCC diagnosis was 49.4 years.

Basic characteristics of the cohort are presented in Table 1. We observed that a higher proportion of men in the underweight and obese groups had a fairly significant or significant health problem at conscription assessment, than in the normal weight and overweight groups. The obese group had a statistically significant higher systolic and diastolic blood pressure. Men in the overweight and obese groups performed better in muscular strength tests than men in the normal weight and underweight groups. In physical capacity tests, the normal weight, overweight and obese groups performed better than the underweight group.

In multivariable adjusted models (Table 2), we observed that overweight men experienced a statistically significant 76% increased risk for RCC than normal weight men (HR: 1.76; 95% CI 1.16–2.67), while obese men experienced a statistically significant 2.87-fold higher risk (HR: 2.87; 95% CI 1.32–6.25). Adjustment tended to attenuate the estimates slightly (see additional models in Supporting Information Table S1). We observed a trend for higher RCC risks with increasing BMI among the young men; one unit increment in BMI conferred a 6% increased risk in RCC (95% CI 1.01–1.10).

We also observed that taller men had an increased risk of RCC compared to shorter men; the two highest quintiles had a hazard ratio for RCC of 1.62 (95% CI 1.11–2.36) and 1.53 (95% CI 1.02–2.30), respectively.

RCC was not associated with indicators of childhood socioeconomic position or with health status, blood pressure, a marker of inflammation (erythrocyte sedimentation rate), cognitive function, muscle strength of physical working capacity measured at conscription (data not shown). In a stratified analysis

Table 1. Characteristics of the study population (n = 238,788) by body mass index (BMI, kg/m^2)

	Underweight (BMI <18.5) N = 27,793 N (%)	Normal Weight (BMI 18.5 to <25) N = 193,166 N (%)	Overweight (BMI 25 to <30) N = 15,507 N (%)	Obese (BMI ≥30) N = 2,322 N (%)	*p* Values
Age at conscription					
Mean ± SD	18.5 ± 0.58	18.5 ± 0.58	18.6 ± 0.58	18.6 ± 0.58	<0.001[a]
*Parental SEI **1960***					
Manual workers	11,379 (41.0)	78,931 (40.9)	7,267 (46.9)	1,110 (47.8)	<0.001[b]
Agricultural workers	999 (3.6)	7,360 (3.8)	728 (4.7)	136 (5.9)	
Farm owners/managers	2,170 (7.8)	19,955 (10.3)	1,529 (9.9)	214 (9.2)	
Office workers	8,488 (30.5)	54,309 (28.1)	3,401 (21.9)	437 (18.8)	
Business owners/managers	2,977 (10.7)	20,968 (10.9)	1,635 (10.5)	263 (11.3)	
Other/unknown	1,780 (6.4)	11,643 (6.0)	947 (6.1)	162 (7.0)	
*Household crowding **1960***					
≤2 people/room	21,593 (77.7)	151,792 (78.6)	11,912 (76.8)	1,721 (74.1)	<0.001[b]
>2 people/room	6,200 (22.3)	41,374 (21.4)	3,595 (23.2)	601 (25.9)	
Health status at conscription					
No diagnosis	10,616 (38.2)	89,086 (46.1)	6,083 (39.2)	267 (11.4)	<0.001[b]
No serious health problem	11,517 (41.4)	75,517 (39.1)	6,805 (43.9)	1,300 (56.0)	
Fairly significant health problem	2,523 (9.1)	13,891 (7.2)	1,252 (8.1)	359 (15.51)	
Significant health problem	3,137 (11.3)	14,672 (7.6)	1,367 (8.8)	396 (17.1)	
Systolic blood pressure (mm Hg)					
Mean ± SD	125.1 ± 10.8	127.5 ± 11.0	132.2 ± 11.1	137.1 ± 11.3	<0.001[a]
Diastolic blood pressure (mm Hg)					
Mean ± SD	70.4 ± 8.5	71.5 ± 8.5	74.4 ± 8.8	78.5 ± 9.1	<0.001[a]
Erythrocyte sedimentation rate (mm/h)					
Mean ± SD	3.7 ± 4.0	3.4 ± 3.4	3.4 ± 3.5	3.7 ± 3.6	<0.001[a]
Cognitive function[1–9]					
Mean ± SD	5.2 ± 2.0	5.3 ± 2.0	4.8 ± 2.0	4.5 ± 2.0	<0.001[a]
Muscular strength[1–9]					
Mean ± SD	3.9 ± 1.1	5.4 ± 1.7	6.5 ± 1.9	6.9 ± 1.9	<0.001[a]
Physical working capacity[1–9]					
Mean ± SD	4.8 ± 2.0	6.5 ± 1.6	6.9 ± 1.7	6.6 ± 1.7	<0.001[a]

a = *p* Value from ANOVA test, b = *p* Value from Chi-square test.

Table 2. Hazard ratio (HR) with 95% confidence interval (CI) for the association between body mass index (BMI), blood pressure and height, and renal cell carcinoma, n = 238,788

	Cohort N (%)	Case N (%)	Unadjusted model HR (95% CI)	Adjusted model[2] HR (95% CI)
BMI				
Underweight (<18.5)	27,793 (11.6)	34 (12.8)	1.16 (0.81–1.68)	0.98 (0.66–1.45)
Normal weight (18.5 to <25)	193,166 (80.9)	198 (74.4)	1.00 (ref)	1.00 (ref)
Overweight (25 to <30)	15,507 (6.5)	27 (10.2)	1.72 (1.15–2.57)	1.76 (1.16–2.67)
Obese (≥ 30)	2,322 (1.0)	7 (2.6)	3.06 (1.44–6.50)	2.87 (1.32–6.25)
BMI[1] (per **1** kg/m^2 increase)	19.5 ± 2.2	21.5 ± 3.2	1.04 (0.99–1.09)	1.06 (1.01–1.11)
Systolic blood pressure[1] (per **1** mmHg change)	127.6 ± 11.1	128.3 ± 12.0	1.01 (0.96–1.02)	1.01 (0.99–1.02)
Diastolic blood pressure[1] (per **1** mm Hg change)	71.6 ± 8.6	71.5 ± 8.9	0.99 (0.99.1.01)	0.99 (0.98–1.01)
Height quintile (cm)				
144–173	49,915 (20.9)	49 (18.4)	1 (ref)	1 (ref)
174–177	52,729 (22.1)	44 (16.5)	0.85 (0.56–1.27)	0.90 (0.59–1.35)
178–180	44,063 (18.5)	48 (18.0)	1.11 (0.74–1.66)	1.21 (0.81–1.81)
181–184	48,522 (20.3)	69 (25.9)	1.45 (1.01–2.10)	1.62 (1.11–2.36)
185–210	43,559 (18.2)	56 (21.2)	1.32 (0.90–1.95)	1.53 (1.02–2.30)

[1]Mean ± SD.
[2]Adjusted for age at conscription, household crowding, parental SEI, systolic blood pressure, diastolic blood pressure, height, health status at conscription, ESR, EVF, muscular strength, physical working capacity, cognitive function.

(Table 3), we found that the association between BMI and RCC was of highest magnitude for men with BMI ≥25 that performed at the lowest physical working capacity (HR: 9.06; 95% CI 2.33–35.27). A sensitivity analysis, where men with reported significant health problems (n = 19,572) were excluded, showed results similar to the results of the main analysis.

Discussion

To the best of our knowledge, this large cohort study is one of the first to show an association of overweight or obesity during adolescence and RCC risk later in life after taking indicators of socioeconomic position during childhood, health status including blood pressure, and other measures in adolescence into consideration. The highest magnitude association was observed among men with the lowest physical working capacity, suggesting that men with a high fat mass (rather than a high muscular mass) constitute a particular high-risk group.

Established risk factors of RCC include obesity, hypertension and cigarette smoking,[2,17,18] but previous research has largely focused on adult exposure to risk factors. For example, a meta-analysis of studies among adults showed that a 5 kg/m^2 increase in BMI increases the risk of RCC by 24% and 34% for men and women, respectively.[4] The role of BMI during adolescence in RCC risk is less well studied, and to our knowledge only one larger longitudinal cohort study has addressed this question before.[19] The present study confirms the findings of

Table 3. Stratified Cox-analyses by physical working capacity showing Hazard ratios (HR) with 95% confidence interval (CI) for the association between body mass index (BMI) and renal cell carcinoma, n = 238,788

	Cohort N (%)	Case N (%)	Unadjusted HR (95% CI)	Adjusted[1] HR (95% CI)
*Lowest working capacity (**1–3**)*				
BMI <18.5	5,477 (42.3)	6 (31.6)	0.78 (0.28–2.15)	0.58 (0.20–1.68)
BMI 18.5 to <25	7,131 (55.0)	10 (52.6)	1.00 (ref)	1.00 (ref)
BMI ≥25	349 (2.7)	3 (15.8)	6.11 (1.68–22.20)	9.06 (2.33–35.27)
*Moderate working capacity (**4–6**)*				
BMI <18.5	18,486 (15.6)	25 (18.1)	1.26 (0.81–1.95)	1.25 (0.79–1.99)
BMI 18.5 to <25	93,137 (78.5)	98 (71.0)	1.00 (ref)	1.00 (ref)
BMI ≥25	7,027 (5.9)	15 (10.9)	2.06 (1.20–3.54)	1.87 (1.06–3.30)
Highest working capacity (7–9)				
BMI <18.5	3,830 (3.6)	3 (2.8)	0.79 (0.25–2.48)	0.71 (0.22–2.27)
BMI 18.5 to <25	92,898 (86.6)	90 (82.5)	1.00 (ref)	1.00 (ref)
BMI ≥25	10,453 (9.8)	16 (14.7)	1.61 (0.94–2.72)	1.61 (0.92–2.81)

[1]Adjusted for age at conscription, household crowding, parental SEI, systolic blood pressure, diastolic blood pressure, height, health status at conscription, ESR, EVF, muscular strength and cognitive function.

the previous and allowed for a considerably longer follow-up time (35.4 *vs.* 15.9 years), thus adding weight to the idea that the risk of RCC may be independently determined by overweight and obesity already during late adolescence.

Overweight and obesity is increasing globally among both children and adults, and has been linked to several forms of cancer including RCC.[1,4] In 2015, approximately 2.3 billion were overweight, and 700 million adults were obese worldwide.[20] The mechanisms behind the association between adiposity and increased cancer risk are however not fully understood. Current theories include oncogenic effects of chronic inflammation, influence of hormones such as leptin and adiponectin, as well as increased levels of oestrogen and overstimulation of insulin- and IGF-I receptors.[21]

Obesity is associated with insulin resistance and increased levels of growth factors such as insulin-like growth factor (IGF)-I. The IGF pathway may be especially important for clear cell RCC which is strongly related to the von Hippel–Lindau (VHL) tumour suppressor gene, which in turn helps regulate IGF-I-mediated cell signalling.[22] VHL is a critical player in renal carcinogenesis, especially for clear cell type. The VHL gene is directly related to IGF-I-mediated cell signalling, which in turn is inhibited in the presence of the intact VHL gene.

Adiponectin, an adipokine involved in regulating glucose and fatty acid metabolism with anti-inflammatory and antiproliferative features, is inversely associated with RCC.[23] Adiponectine is reduced by adipose tissue hypoxia and oxidative stress,[10] especially so in central fat distribution and increases in serum by weight loss.[24] Obese children also have lower serum adiponectin levels.[25]

Hypertension is another established risk factor for RCC.[26] Even though we observed that obese men had a higher systolic and diastolic blood pressure at conscription assessment compared to normal weight men, it was not an independent risk factor for RCC.

It has been discussed to what extent BMI is an appropriate measurement of adiposity, as it does not differentiate between fat mass and fat-free mass. Dual- energy X-ray absorptiometry (DEXA) is currently regarded as the gold standard to define obesity, but the method is expensive and complex. A strong correlation between BMI and body fat measured by DEXA in children and adolescents has, however, been demonstrated.[27] We further observed that the obese and overweight young men in our cohort performed better than normal and underweight men in physical working capacity and muscular strength tests, indicating that their high BMI might be a result of high muscular mass rather than fat mass, and that BMI might not be an ideal measurement of adiposity in this group. However, the increased risk of RCC for obese as well as overweight men remained when we adjusted for physical working capacity and muscular strength.

We also observed that taller men had an increased risk of RCC. Increased adult height has been linked to increased risk of several cancers including RCC where a meta-analysis demonstrated a 10 % increased risk of kidney cancer per five cm increased height.[28] Height has been suggested to serve as a marker for genetic, environmental, hormonal, and nutritional factors affecting growth. Taller persons may have been exposed higher levels of insulin, IGFs and pituitary-derived growth hormones during childhood and adolescence which could be mechanisms of cancer development.[29] Another theory is that taller persons have more cells and that their tissues thus undergo more cell divisions, increasing the risk of DNA error and consequent malignant development.[30]

Strengths of this population-based study include its size, prospective design and the long follow-up that spans more than three decades. Some potential limitations should, however, be mentioned. Despite the long follow-up, the maximum age at the end of follow up was only 57 years. The incidence of RCC increases with age and reaches a plateau around 70 years[3] and our follow-up period does thus not cover the ages with the highest incidence rates. The aetiology of our cases of early-life RCC could differ from those occurring later in life, and the results may therefore not be directly generalizable to older populations. Also, the total number of RCC diagnoses is limited, rendering low numbers in the stratified analysis. The study is based on men only.

Another potential weakness is the lack of data on smoking. A meta-analysis of 24 studies reported a relative risk of RCC to 1.38 for ever smokers compared to lifetime never-smokers.[31] Given its magnitude, however, the association is unlikely to completely explain the association observed between overweight/obesity and risk of RCC.

We further lack information about BMI after military conscription as well as about dietary habits later in life. We are thus unable to disentangle the potential influence of the total duration of time being overweight/obese from that of being obese in adolescence. There is some evidence that a diet with high glycemic load increases the risk of RCC,[32] and it is thus possible that the observed pattern is explained by childhood dietary intake. Even if the link between early overweight/obesity can be confirmed, intervention studies of weight-loss among adolescents are needed before any firm conclusions regarding the effect of weight-loss among teenagers on their future risk of RCC can be made.

Conclusion

Data from this this population-based cohort study show a clear association between higher BMI during adolescence and subsequent risk of RCC, suggesting that overweight and obesity play a role in RCC pathogenesis as early as during adolescence. The rationale underlying efforts to reduce childhood and adolescent obesity may thus extend to include prevention of RCC. The findings of this study suggest that the link between overweight/obesity and renal cell carcinoma is already established in late adolescence.

Authors' contributions

K.F. and S.M. designed the study; A.F., S.M., and K.F. acquired and prepared the data; A.F. analysed the data; A.L., P.S., S.M., A.F., K.F. interpreted the data; P.S. and

K.F. supervised the study. A.L. wrote the first draft of the manuscript to which all authors made significant subsequent contributions. All authors approved the final version of the manuscript. KF had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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